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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,423	10/12/2001	Kirk Hogan	HOGAN-06650	2436

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/976,423	HOGAN, KIRK	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed March 16, 2007. Currently, claims 72-112 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 72-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) and Pharmacogenetics (Chapter 4, pages 309-326) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) and further in view Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) and Anderson et al (US Pat. 6,267,722, July 31, 2001).

It is noted that these claims contain a preamble which recites an intended use, however, it is also noted that this use does not confer patentable weight on the product claims since the preamble does not materially change what is present in the kit itself

and thus represents an intended use of the kit (see MPEP 2111.02). Further, with regard to the limitation that the kits contain instructions for using said kit for generating said perioperative genomic profile for said subject, the inclusion of instructions is not considered to provide a patentable limitation on the claims. See In re Ngai, 367 F.3d 1336, 70 U.S.P.Q.2d 1862 (Fed. Cir. 2004) (holding that an inventor could not patent known kits by simply attaching new set of instructions to that product).

Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent. SC and mivacurium are potentially toxic in people with **BchE** deficiency. AAS teaches that the principles of molecular biology tests and their application to BchE variants are well illustrates and anesthesiologists need to keep up to date about these applications. AAS also teaches that other hereditary conditions of special interest to anesthesiologists, such as malignant hyperthermia, may be diagnosed by similar methods in a few years (page 141).

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). La Du teaches specific variants in the Butyrylcholinesterase gene.

Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of **CYP2D** gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches that the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that "inherited differences in drug-metabolizing capacity are generally monogenic traits and their influence on the pharmacokinetices and pharmacologic effects of medications is determined by their importance for the activation or inactivation of drug substrates (page 487, col. 2). Evans also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for

nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1). Evans specifically suggests making a DNA array for automated, high-throughput detection of functionally important mutation in genes that are important determinants of drug effects such as drug-metabolizing enzymes. The suggested genes on the array include **TNF, MTHFR and CYP2D6**, for example (see figure 3).

Thus, the prior art clearly illustrates that the claimed genes are known to be related to resistance to anesthesia.

Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays. Hoon teaches using multiple markers provides increased sensitivity (abstract). Hoon teaches that marker combinations may be developed, which are particularly sensitive to the effect of therapeutic regimens on disease progress such that patients may be monitored (col. 4, lines 65-68). In a particular example, Hoon demonstrates that number of markers was studied and that using four markers was significantly better than a single marker alone (col. 21).

Additionally, Hacia teaches mutational analysis using oligonucleotide microarrays. Hacia teaches that arrays of 1,480 oligonucleotide probes were designed to detect 37 known mutations, probes were spotted on surfaces to detect mutations in HBB, and BRCA1. Hacia teaches that arrays of 135,000 probes were used to

interrogate the entire 16.6kb human mitochondrial genome from ten samples (page 44, col. 1). Chips have also been used for the simultaneous genotyping of 500 markers (page 45, col. 1). Hacia teaches that chips allow for unprecedented throughput in mutational analysis with a high degree of accuracy (page 46, col. 2). Hacia illustrates the design of probes and oligonucleotides for detection of single nucleotide substitutions and variations. As seen in Figure 3, for example, 25 overlapping 25-base probes are affected by changes in a single target nucleotide. Moreover, Hacia teaches that the analysis is completed by scanning for variation and evaluation using an algorithm (page 44)(i.e. a computer program directing the processor to analyze the data). As seen in Figure 5, the data is outputted from a computer program to illustrate the detection of polymorphisms.

Finally, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already come prepared. Ahern teaches kits may comprise instructions that provide researcher detailed instructions to follow.

Anderson et al. (US Pat 6,267,722, July 31, 2001) teaches point of care diagnostic systems. Anderson teaches the systems are designed to accept input in the form of patient data, including, but not limited to biochemical test data, physical test data, historical data and other such data, and to process and output information, preferably data relating to a medical diagnosis or a disease risk indicator. The patient data may be contained within the system, such as medical records or history, or may be input as a signal or image from a medical test or procedure, for example, immunoassay

test data, blood pressure reading, ultrasound, X-ray or MRI, or introduced in any other form. Specific test data can be digitized, processed and input into the medical diagnosis expert system, where it may be integrated with other patient information. The output from the system is a disease risk index or medical diagnosis.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the necessary reagents for sampling patients prior to subjecting the patient to anesthetics for the presence of alleles within the CYP2D6, or BCHE genes which cause resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, as taught by Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, or Evans and thus avoiding any fatal reaction to the anesthesia, for example.

As discussed above, AAS teaches that SC and mivacurium are potentially toxic in people with BchE deficiency. La Du et al teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine and the variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches that codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. Evans also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that

require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3).

Moreover, given the teachings of Hoon and Hacia that sampling multiple markers provides increase sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery. Therefore, the skilled artisan would have additionally analyzed a patient for a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, or Evans. Given the state of the art with relation to known markers and detecting the markers as indicative of certain disease which either trigger episodes when exposed to anesthetics, or are poor metabolizers or potentially cause thrombosis are well known. The ordinary artisan would have been motivated to have packaged reagents needed to screen individuals to determine the genetic composition of the individuals to provide individualized diagnosis and to avoid any fatal reaction to the anesthesia in a quick and efficient cost effective kit.

Hacia teaches that large numbers of probes are placed on arrays for the express benefit of high-throughput mutational analysis with a high degree of accuracy (page 46, col. 2). The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine

whether plausible substitutes may be provided to patients which would not cause these conditions to arise. Specifically, codeine should be administered with care to individuals having certain BchE mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patients genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

In summary, the prior art teaches

* Numerous mutations in numerous genes which are associated with toxicity, decreased or increased efficiency, ineffective to various operative drugs (De Lu, AAS, Poort, Evans, for example)
* Methods using multiple markers provide increased sensitivity over methods employing single markers (see Hoon)
* Arrays for high-throughput and highly accurate mutational analysis which may be used for as many as 500 mutations (Hacia)
- Packaging reagents into a kit saves time and money (Ahern)
- The prior art teaches the use of computer programs for systems of diagnostic care for outputting patient information and risk index (Anderson)

Thus, the ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, or Evans and Hacia and Hoon which are necessary for determining the genotypes of BchE and CYP2D6 which are associated poor reactions to anesthesia into a kit, as taught by Ahern for the express purpose of saving time and money and included a computer program taught by Anderson for the digitization, integration and convenience of patient information, and risk index.

Response to Arguments

The response traverses the rejection.

The response asserts a prima facie case of obviousness requires the examiner to cite reference which (b) suggests or motivates one of ordinary skill in the art to combine the claimed elements to yield the claimed invention. This argument is incorrect. *KSR v. Teleflex*, 550 U. S. ____ (2007): In a unanimous opinion authored by Justice Kennedy, the Supreme Court held that the Federal Circuit's "narrow" & "rigid" TSM test is not the proper application of the nonobviousness doctrine of Section 103(a) of the Patent Act. "To facilitate review, [the obviousness] analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ." An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __ (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Thus, given KSR, the references are not specifically required to provide the motivation. The teaching suggestion and motivation may be the common sense of those skilled in the art would employ. Thus, as is here, the ordinary artisan would be motivated to have gathered the reagents necessary for determining alleles associated

with poor outcomes to surgery into a kit for the benefits of a kit. Moreover, including a computer program for the expected benefits of digitizing, processing and inputting the information into the medical diagnosis expert system, where it may be integrated with other patient information. The output from the system is a disease risk index or medical diagnosis.

The response suggests that the references did not teach or suggest a computer program comprising instructions which direct a processor to analyze data derived from said reagents. Although the examiner believes In re Ngai specifically speaks to this issue, in an effort to provide that computers for obtaining data, synthesizing the data and then outputting information for risk index were known at the time the invention was made, Anderson was made of record in the instant application. While the response asserts that silence in the Board's decision is acquiescing to applicant's position, this argument has been reviewed but is not persuasive, as there is no indication of the Board's position on this matter or record.

5. Newly Added Claims 108-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11,, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and

further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) and further in view Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) and Anderson et al (US Pat. 6,267,722, July 31, 2001) as applied to 72-107 above and further in view of the specification (Tables 1-4).

Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia do not specifically teach profiling for each of BchE, CYP2D6, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, CTP2, TNFA and TNFB.

The instant specification teaches markers in each of these genes which are associated with various operative related disorders. The specification clearly illustrates genes and mutations which are associated with the particular mutations. The response filed March 26, 2001 specifically illustrates that the invention does not claim discovery of newly identified DNA sequences (page 7).

Therefore, it would have been obvious in view of the teachings of Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia to include any number of genes on the array of Hacia for the highthroughput analysis of operatives complications.

Conclusion

6. No claims allowable over the art.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
June 8, 2007